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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,213	08/13/1999	DAVID STERN	59472/JPW/SH	3469

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EXAMINER
WEGERT, SANDRA L

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/19/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/374,213	STERN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,44,46 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41, 44, 46, 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Supplemental Information Statement with attached references and the International Search Report, submitted 24 September 2001, were entered as Paper 8.

The amendment filed 30 July 2002 (Paper No. 12) has been entered. Claims 1-26, 34-40, 42, 43, 45 and 47-54 have been cancelled. Claim 55 was amended. Claims 41, 44, 46 and 55-58 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

Claim Objections

The objections to Claims 45 and 55 because they recite or encompass non-elected inventions, as recited in the previous Office Action (5 July 2001; p. 3), is *withdrawn*. Applicants have amended Claim 55 to recite only the elected cell type and have cancelled Claim 45 (Paper 12, 15 July 2002).

Information Disclosure Statements

The requirement for a complete Information Disclosure Statement, as set forth at p. 4 of the previous Office Action (Paper 11, 9 April 2002), is *withdrawn* in view of Applicant's explanation that the Information Disclosure Statement, submitted as Paper 4, was entered previously (12/29/99).

The Supplemental Information Statement with attached references and the International Search Report, submitted 24 September 2001, have been entered as Paper 8.

35 USC § 103(a), Obviousness.

The rejection of claims 41, 44, 46 and 55-58 under 35 U.S.C. 103(a), as recited in the previous Office Action (Paper 11, 9 April 2002), is *withdrawn.* Claims 41, 44, 46 and 55-58 were rejected under 35 U.S.C. 103(a) as being unpatentable over Miyata, et al (1996, J. Clin. Invest., 98: 1088) in view of Yan, et al (1997, PNAS, 94: 5296). As pointed out by the Applicant, the amendment submitted 26 March 2001 (Paper 6), established priority to an application filed 26 January 1996. Therefore, the Yan, et al paper (called the "Miyata" paper by the Applicant as well as by the Examiner in the previous Office Action) cannot be used as prior art for the instant Application.

Maintained Rejections/Objections

Figures

The objections to the Figures as recited in the previous office action (5 July 2001; p. 3)- is maintained. Applicants have indicated that they will submit formal drawings in the event there are allowable claims.

35 USC § 112, First-paragraph.

The rejection of claims 41, 44, 46 and 55-56 under 35 U.S.C. 112, first paragraph, as recited in the previous Office Action (Paper 11, 9 April 2002), is *maintained.*

The Specification discloses using the soluble form of the receptor to inhibit binding of amyloid to *RAGE* in PC12 cells transfected with *RAGE.* The disclosure also describes using the methods of the Invention to inhibit binding of amyloid to splenic cells of mice, as measured by cellular changes in NFκB, for example. The Examiner stressed that there is no link described in the disclosure that connects inhibition of amyloid in splenic cells of mice to a method of treating a *Subject* or disease *in vivo*, as applicable to human beings.

Applicants discuss both in vitro data (pp 63-64 of the Specification) and in vivo data (p 57 of the Specification) and argue that "in vitro data demonstrate that rage interacts specifically with Aβ fibrils and that the blockade of RAGE completely suppressed symptoms of cellular stress such as fibril-dependent NF-κB activation and DNA fragmentation completely" (p. 9, 30 July 2002, Paper 12). In discussing the in vivo data, Applicants point out "in vivo administration of sRAGE blocked amyloid fibril-RAGE interactions and suppressed cellular stress and amyloid fibril accumulation in tissues" (p. 10, 30 July 2002, Paper 12). Applicant has argued that use of s*RAGE* to block peripheral amyloidosis in a mouse model is an example of an enabling in vivo use (Paper 10, 23 January 2002, p. 16). Applicant also argued that

accumulation of amyloid in the spleens of mice, the association of increased amyloid with IL-6 production (p 21), and its blockade by administration of sRAGE in a dose-dependent manner, are evidence that the methods described in the instant Specification can be applied to increased amyloidosis (as evidenced by a measure of cell stress) associated with disease in humans. For example, the Picciotto, et al paper (1998, Physio. Rev. 78: 1131) was submitted by the Applicant to support the argument that mice models of Alzheimer's disease are relevant and enabling for the claimed Invention (Paper 10, 23 January 2002).

Applicant's arguments (Paper 12, 30 July 2002) have been fully considered but are not deemed to be persuasive for the following reasons:

There exist several problems with using mouse models of Alzheimer's Disease, in which there are defects in amyloid processing, to predict whether a therapy in human subjects will be effective. As discussed previously (Paper 11, 9 April, 2002) tests of learning and memory in animals cannot be seen to reflect the cognitive deficits seen in humans with disease related to amyloid deposition. The experiments listed in the instant Specification (see, for example, pp 8-17) use soluble RAGE to inhibit binding of amyloid to splenic cells of "AEF"mice (mice injected with *AEF* to induce amyloid production). However, eliminating amyloid deposition and damage in mice splenic cells, by using soluble RAGE, is several steps removed from treating a human subject for a disease related to amyloidosis. Furthermore, deficits that distinguish Alzheimer's diseases from other amyloid diseases or from more localized causes of cerebral damage (i.e, stroke) cannot be adequately evaluated by means of this animal model. In addition, the art is silent as to the possible contribution of the *AGE* receptor to both the pathogenesis of

animal amyloidosis and Alzheimer's disease, thus poorly predictive of a method of treatment involving *RAGE* or *sRAGE*.

Similarly, the rejection of claims 57 and 58 under 35 U.S.C. 112, first paragraph, as recited in the previous Office Action (Paper 11, 9 April 2002), is *maintained.* The claims read on using s*RAGE* to inhibit binding of ligand and thus modulate a disease state involving β-sheet fibrils. The Specification discloses using the soluble form of the receptor to inhibit binding of amyloid to *RAGE* in PC12 cells transfected with *RAGE*. The disclosure also describes using the methods of the Invention to inhibit binding of amyloid to splenic cells of mice, as measured by cellular changes in NFκB, for example.

Applicant's arguments rely on the fact that "in vivo administration of sRAGE blocked amyloid fibril-RAGE interactions and suppressed cellular stress and amyloid fibril accumulation in tissues" (p. 12, 30 July 2002, Paper 12). Applicant has argued that use of s*RAGE* to block peripheral amyloidosis in a mouse model is an example of an enabling in vivo use (Paper 10, 23 January 2002, p. 16), and that furthermore in "a model of systemic amyloidosis, blockade of fibril-RAGE interaction in vivo suppressed cellular stress and amyloid A fibril accumulation" (p. 12, 30 July 2002, Paper 12). Applicant also argued that accumulation of amyloid in the spleens of mice, the association of increased amyloid with IL-6 production (p 21), and its blockade by administration of sRAGE in a dose-dependent manner, are all evidence that the methods described in the instant Specification can be applied to increased amyloidosis (as evidenced by a measure of cell stress) associated with disease in humans. For example, the Picciotto, et al paper

(1998, Physio. Rev. 78: 1131) was submitted by the Applicant to support the argument that mice models of Alzheimer's disease are relevant and enabling for the claimed Invention (Paper 10, 23 January 2002).

The Applicant has argued that use of s*RAGE* to specifically block amyloid formation in vitro, as well as the fact that one could use in vitro data together with in vivo data in the literature, as *a whole* demonstrate the ability of the disclosed invention to modulate a disease state. The applicant argues that the specification discloses "common denominators of fibrillar pathologies" (Specification, page 80).

The Examiner maintains that there is no nexus described in the disclosure that would enable the methods of the Invention as applied to Alzheimer's disease or a disease related to amyloidosis or to inhibiting binding of ligand to *RAGE* in a diseased subject. No data are referred to in the Specification or in the literature that demonstrate the processes described and claimed as pertaining to Alzheimer's disease, or a disease of amyloidosis, or to use in *subjects*, for example. Importantly, there is no evidence presented of the *chain of events* that presumably links amyloid to Alzheimer's disease by means of RAGE. In addition, using the methods of the Invention to inhibit binding of amyloid to transfected cells or splenic cells of mice, as measured by changes in NFκB, for example, is not shown to be further linked to preventing a disease process.

Conclusion: Claims 41, 44, 46, and 55-58 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sandra Wegert
11/17/02

Elizabeth C. Kemmerer